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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/529,762	RITTERSHAUS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

--Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *3/13/03*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*.

Claim(s) objected to: *None*.

Claim(s) rejected: *40-48 and 51-52*.

Claim(s) withdrawn from consideration: *None*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because:

Claims 40-48 and 51-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of increasing the production of anti-CETP antibody wherein the method comprises administering to a rabbit a C-terminus of human CETP peptide conjugated to tetanus toxoid consisting of SEQ ID NO: 7 or a whole recombinant human CETP consisting of SEQ ID NO: 1 (See page 17 lines 2-3 of the specification) for reducing CETP activity, increasing the HDL-cholesterol, and lowering LDL-cholesterol associated with atherosclerosis, does not reasonably provide enablement for (1) a method of modulating the level of endogenous, active cholesteryl ester transfer protein (CETP) in any mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that the untreated mammal, (2) a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a level of essentially 0 mg of CETP per milliliter of blood of the mammal, (3) a method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 90% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (4) the method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (5) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein less than about 10% of the total cholesterol in the blood of the mammal is LDL-cholesterol, (6) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol, (7) the method wherein the mammal is a human, (8) the method wherein any whole, non-endogenous cholesteryl ester transfer protein is any xenogeneic CETP, any allelic variant of any mammalian's endogenous CETP, any mammalianized non-endogenous CETP in which the amino acid sequence of a non-endogenous CETP ahs been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said non-endogenous CETP more similar to the mammal's endogenous CETP, (9) any method mentioned above in combination with an adjuvant such as the ones recited in claim 52 for non-specifically stimulate the immune response of the mammal for a vaccine against LDL-cholesterol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.
The specification discloses only a full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, two mammalianized rabbit CETP polypeptides consisting of SEQ ID NOS: 5 and 6 and a method of vaccinating a rabbit, which is a mammal, with a recombinant human CETP of SEQ ID NO: 1, or a peptide of the C-terminus of human CETP conjugated to tetanus toxoid of SEQ ID NO: 7 (See page 16-17, Figs 8-9 of the specification) for increasing the titer of CETP specific antibodies in the plasma, wherein said antibody cross-react with the rabbit CETP c-terminal peptide from amino acids 477-496 of SEQ ID NO: 3, thereby reducing the CETP activity below 20% of the untreated control at 14 weeks (Fig 9), reducing the level of native CETP to 0 mg/ml of blood of the mammal at 14 weeks post immunization, increasing the level of HDL-cholesterol to greater than 90% of the total cholesterol in the blood of the mammal, increasing the level of HDL-cholesterol to about 100% of the total cholesterol in the blood of the mammal 14 weeks after immunization (Fig 9), reducing the level of LDL-cholesterol of less than about 10% of the total cholesterol in the blood plasma of the mammal (See Fig 7). The specification further discloses on page 5 line 23 that non-endogenous CETP can be from another mammalian species such as rabbit CETP, mouse CETP or simian CETP for administration to a human.
Other than the specific polypeptides mentioned above for a method of inhibiting the endogenous CETP activity, the specification fails to provide any guidance as how to make and use any non-endogenous CETP for a method of modulating any endogenous CETP in any mammal. There is insufficient guidance and working examples as to which amino acid residues within any of the non-endogenous CETP of any mammal can be deleted, substitute and whether the resulting modified CETP protein would maintain the structure and function as SEQ ID NO: 7 and 1, in turn, generating antibodies that would bind specifically to the human or the rabbit CETP for a method of inhibiting any endogenous CETP activity associated with atherosclerosis. Given the indefinite number of undisclosed non-endogenous CETP protein, it is unpredictable which undisclosed non-endogenous CETP would be useful for a method of inhibiting any non-endogenous CETP activity associated with atherosclerosis.
Ngo et al teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).
It is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in antibody specificity that differs from antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which antibody response generated from any CETP polypeptide and fragment thereof will have the same antibody specificity as an antibody generated from the SEQ ID NO: 1 and 7, in turn, can be use for a method of reducing CETP activity associated with atherosclerosis.
Furthermore, Marrott et al (PTO 1449) teach that transgenic mice expressing exogenous simian cholesteryl ester transfer protein (CETP) results in severe atherosclerosis with a marked increases in the concentration of LDL-cholesterol and a decrease in the concentration of HDL-cholesterol (See entire document, Abstract, in particular). Likewise, Breslow et al (PTO 1449) teach human CETP transgenic

mice overexpressing human CETP has lower level of HDL-cholesterol the effects CETP were less than expected based on studies comparing normal and CETP-deficient humans (See page 8316, column 2, CETP transgenic mice, in particular). These results indicate that not all xenogeneic none-endogenous CETP are appropriate for a method of modulating CETP activity, particularly in humans, where atherosclerosis is multi-factorial complex disease.

With regard to allelic variant of any mammal's endogenous CETP, the specification defines allelic variant is a polymorphism of human CETP producing by another human individual (See page 8, lines 20 of the specification). However, the specification discloses only one human CETP polypeptide consisting of SEQ ID NO: 1. There are no additional human CETP which have been demonstrate to be useful for immunizing any mammal, in turn, for a method of modulating any endogenous CETP within any mammal. Given the indefinite number of undisclosed non-endogenous CETP protein, it is unpredictable which undisclosed non-endogenous CETP would be useful for a method of inhibiting any non-endogenous CETP activity associated with atherosclerosis. It follows that any xenogeneic CETP, any allelic variant of any mammalian's endogenous CETP, any mammalianized non-endogenous CETP other than SEQ ID NO: 5 and 6 are not enable.

Regarding claims 46 and 48 wherein the mammal is a human, there are no working examples in the specification as filed to demonstrate that administering any whole non-endogenous CETP such as recombinant human CETP is effective in reducing CETP activity below 20% of that untreated human, reducing the level of essentially 0 mg of CETP per ml of blood of the human, increasing the level of HDL-cholesterol to greater than about 90% or about 100% of the total cholesterol in the blood of the human, lowering the level of LDL-cholesterol to less than 10% of the total cholesterol in the blood plasma or reducing the level of LDL-cholesterol to essentially none as recited in claim 45. Furthermore, since CETP is a "self" protein, it is not clear in the specification as filed how administering a whole recombinant human CETP (which is not foreign and no different than one's own CETP) would induce endogenous antibody direct toward one's own CETP at a level sufficient high to modulate one's own level of endogenous CETP activity. Stevens et al teach in order induce high levels of antibodies reactive to one's own protein (break immune tolerance) such as hCG for a contraceptive vaccine, the protein must be conjugated to a foreign protein or carrier molecule such as KLH or tetanus toxoid to enhance the immunogenicity of the hCG protein. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 3/13/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Applicants' claims are directed to methods of using a whole, non-endogenous CETP to produce anti-atherogenic condition such as an unexpectedly low level of circulating CETP molecules (essentially no detectalbe CETP per ml of blood plasma) or of CETP activity (below 20% of the activity in an untreatd mammal), an unexpectedly high level of HDL-cholesterol (greater than 90% and as high as 100%) and unexpectedly low level of LDL-cholesterol (less than 10% and as low as, essentially, none); (2) a patent specification needs not teach every known mammalian CETP sequence, (3) what is claimed is a method for modulating one of these levels mentioned above by administering a whole, non-endogenous CETP to a subject so as to achieve such unexpected results, (4) it is incumbent on the Examiner to explain and provide evidence in support of his contention that the person skilled in the art is incapable of knowing what is well known in the art, incapable of following the steps of Applicants' working examples, and incapable of uisng Applicants' model as a model for other methods encompassed by the claims.

In response, the issue here is whether administering any "non-endogenous CETP" or any "allelic variant" of any mammal's endogenous CETP, or any "mammalianized, non-endogenous CETP in which the amino acid seuqence has been altered by deletion, or substitution of one or more amino acids" could produce antibodies that react with the mammal's endogenous CETP as a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) activity such as reducing "CETP activity" below 20% of that untreated mammal, or less than 10% of the total cholesterol in the blood plasma of the mammal is LDL-cholesterol, or 0 microgram of CETP per ml of blood of the mammal, or greater than about 90% or 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol, or essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol wherein the mammal is human. The term "non-endogenous CETP" as defined on page 5 of the specification as "xenogenic CETPS....such non-endogenous CETP can be CETP of simian CETP, allelic variation or polymorph of a mammalian CETP, or CETP from one species modified to have an amino acid sequence more similar to the native CETP of another species (e.g., a "humanized rabbit CETP) for administration to human.

The specification discloses only a full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, two mammalianized rabbit CETP polypeptides consisting of SEQ ID NOS: 5 and 6 and a method of vaccinating a rabbit, which is a mammal, with a recombinant human CETP of SEQ ID NO: 1, or a peptide of the C-terminus of human CETP conjugated to tetanus toxoid of SEQ ID NO: 7 (See page 16-17, Figs 8-9 of the specification) for increasing the titer of CETP specific antibodies in the plasma, wherein said antibody cross-react with the rabbit CETP c-terminal peptide from amino acids 477-496 of SEQ ID NO: 3, thereby reducing the CETP activity below 20% of the untreated control at 14 weeks (Fig 9), reducing the level of native CETP to 0 mg/ml of blood of the mammal at 14 weeks post immunization, increasing the level of HDL-cholesterol to greater than 90% of the total cholesterol in the blood of the mammal, increasing the level of HDL-cholesterol to about 100% of the total cholesterol in the blood of the mammal 14 weeks after immunization (Fig 9), reducing the level of LDL-cholesterol of less than about 10% of the total cholesterol in the blood plasma of the mammal (See Fig 7). The specification further discloses on page 5 line 23 that non-endogenous CETP can be from another mammalian species such as rabbit CETP, mouse CETP or simian CETP for administration to a human.

The specification does not teach how to make and use any non-endogenous CETP mentioned above because there is no guidance as to which amino acid within full length amino acid sequence of any mammalian CETP could be altered by substition, or deletion and whether the resulting non-endogenous CETP maintain both structure and function, in turn, would generate antibody that is specific for the endogenous mammalian CETP as a method of "modulating" CETP activity.

The term "non-endogenous CETP" has no structure, much less function. Without the specific amino acid residues of the non-endogenous CETP, even one skill in the art cannot practice the claimed invention, much less predicting which undisclosed non-

endogenous CETP would generate antibody that will have the same antibody specificity as an antibody generated from the SEQ ID NO: 1, 7, 5 and 6, in turn, can be use for a method of reducing CETP activity associated with atherosclerosis. Further, there is no guidance as to which amino acid residues within the full length amino acid sequence of any undisclosed non-endogenous CETP from any mammal can be deleted, substitute and whether the resulting modified non-endogenous CETP protein would maintain the same structure, much less in generating antibodies that bind specifically to any mammal's endogenous CETP for a method of inhibiting any endogenous CETP activity associated with atherosclerosis. Other than the specific non-endogenous CETP mentioned above, there are no allelic variant of any mammal's endogenous CETP, any mammalianized non-endogenous CETP in which the amino acid sequence of the non-endogenous CETP has been altered such as amino acid substitution, or deletion.
Ngo et al, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).
With regard to any mammalianized non-endogenous CETP in which the amino acid sequence of the non-endogenous CETP has been altered such as amino acid substitution, or deletion, Kuby et al, of record, teach immunizing a peptide (deletion from the full length polypeptide) versus immunizing a protein derived from a full-length polypeptide may result in antibody specificity that differs from antibody specificity directed against the native full-length polypeptide. Further, the term "choesteryl ester transfer protein (CETP) activity in base claim 40 is not defined in the specification and the term "modulating" encompasses increasing and decreasing activity which are mutually exclusive. It is known that even a single amino acid difference can have a drasttic effect on the binding specificity of an antibody. Given the indefinite number of undisclosed "non-endogous CETP", it is unpredictable which undisclsoed non-endogenous CETP, "allelic variant" of any mammal's endogenous CETP, or any "mammalianized, non-endogenous CETP in which the amino acid seuqence has been altered by deletion, or substitution of one or more amino acids" that could produce antibodies that would bind specifically to the mammal's endogenous CETP as a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) activity. For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Claims 40-48 and 51-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a written description of (1) a method of modulating the level of endogenous, active cholesteryl ester transfer protein (CETP) in any mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that the untreated mammal, (2) a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a level of essentially 0 mg of CETP per milliliter of blood of the mammal, (3) a method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 90% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (4) the method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (5) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein less than about 10% of the total cholesterol in the blood of the mammal is LDL-cholesterol, (6) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal any whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol, (7) the method wherein the mammal is a human, (8) the method wherein any whole, non-endogenous cholesteryl ester transfer protein is any xenogeneic CETP, any allelic variant of any mammalian's endogenous CETP, any mammalianized non-endogenous CETP in which the amino acid sequence of a non-endogenous CETP ahs been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said non-endogenous CETP more similar to the mammal's endogenous CETP, (9) any method mentioned above in combination with an adjuvant such as the ones recited in claim 52 for non-specifically stimulate the immune response of the mammal for a vaccine against LDL-cholesterol.

The specification discloses only a full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, a mammalianized rabbit CETP consisting of SEQ ID NOS: 5 and 6 and a method of vaccinating a rabbit, which is a mammal, with a recombinant human CETP of SEQ ID NO: 1, or a peptide of the C-terminus of human CETP conjugated to tetanus toxoid of SEQ ID NO: 7 (See page 16-17, Figs 8-9 of the specification) for increasing the titer of CETP specific antibodies in the plasma, wherein said antibody cross-react with the rabbit CETP c-terminal peptide from amino acids 477-496 of SEQ ID NO: 3, thereby reducing the CETP activity below 20% of the untreated control at 14 weeks (Fig 9), reducing the level of native CETP to 0 mg/ml of blood of the mammal at 14 weeks post immunization, increasing the level of HDL-cholesterol to greater than 90% of the total cholesterol in the blood of the mammal, increasing the level of HDL-cholesterol to about 100% of the total cholesterol in the blood of the mammal 14 weeks after immunization (Fig 9), reducing the level of LDL-cholesterol of less than about 10% of the total cholesterol in the blood plasma of the mammal (See Fig 7).
With the exception of the specific CETP polypeptides mentioned above, there is insufficient written description about the structure associated with functions of any non-endogenous CETP wherein said endogenous CETP is any xenogeneic CETP, any allelic variant of any mammalian's endogenous CETP, any mammalianized non-endogenous CETP having one more amino acid altered by deletion, or substitution as to make the amino acid sequence more similar to the mammal's endogenous CETP for a method of modulating the level of endogenous active cholesteryl ester transfer protein associated with atherosclerosis.
Given the lack of a written description of any additional representative species of allelic variant of any human CETP such as any naturally occurring polymorphism as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure

fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.
Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/13/03 have been fully considered but are not found persuasive.
Applicants' position is that (1) there is an actual reduction to practice of treatment to reduce CETP actiity, raise HDL above 90%, and to lower LDL to less than 10% to essentially none using a whole non-endogenous CETP vaccine according to the description. (2) the specification provides a description of methods of using whole CETP molecule as immunogens, the complete amino acid structure of human and rabbit CETP (SEQ ID NO: 1 and 3) and descriptions of methods for assaying the effectiveness of the vaccine.

In response to Applicants' arguments, other than the specific nonendogenous CETP mentioned above, there is inadequate written description about the structure associated with function of any "non-endogenous CETP", any "non-endogenous CETP" such as any "allelic variant" of any mammal's endogenous CETP, or any "mammalianized, non-endogenous CETP in which the amino acid seuqence has been altered by deletion, or substitution of one or more amino acids" that could produce antibodies that react with the mammal's endogenous CETP as a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) activity such as reducing "CETP activity" below 20% of that untreated mammal, or less than 10% of the total cholesterol in the blood plasma of the mammal is LDL-cholesterol, or 0 microgram of CETP per ml of blood of the mammal, or greater than about 90% or 100% of the total choleste because any endogenous CETP without the specific amino acid sequence or SEQ ID NO has no structure, much less generating antibodies specific for endogenous mamalian CETP as a method of modulating CETP activity.

Claims 40-43, 45, 47 and 51-52 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO 96/39168 publication (Dec 12, 1996, PTO 892).
The 96/39168 publication teaches a method of modulating the endogenous active cholesteryl ester transfer protein (CETP) in a mammal such as a rabbit comprising administering to said mammal a full-length human CETP of SEQ ID NO: 1 of WO 96/39168, or a taxoid conjugated human CETP peptide, which are non-endogenous CETP, in an amount effective to stimulate an immune response such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as reducing the CETP activity below 20% of that of the untreated mammal (See abstract, Fig 2, of WO 96/39168, in particular). The reference method comprises administered to the mammal in combination with an adjuvant such as CFA (Complete Freund's Adjuvant) or IFA (Incomplete Freund's adjuvant) wherein the reference adjuvant is effective to non-specifically stimulate the immune response of the mammal such as production of antibody (See page 7, line 29, page 8, lines 1-2, in particular). The reference method decreases LDL-cholesterol to less than 16% of the total cholesterol in the serum (blood plasma), which is less than 20% (See Table 1, page 11, in particular). Claim 47 is included in this rejection because the reference teaches xenogeneic CETP which is a human CETP, in addition to a mammalianized non-endogenous CETP (See SEQ ID NO: 3 of WO 96/39168) where the reference SEQ ID NO: 3 is common to both human and rabbit CETP, which makes the human CETP more similar to rabbit and vice versa and the epitope is recognized by anti-CETP monoclonal antibody to which it is neutralized (See page 7, lines 20-22, in particular).
While the reference is silent that the reference method of administering to the mammal a whole non-endogenous CETP has the property of that recited in claims 41-43 and 45, the antibody directed against said non-endogenous CETP in the mammal and the functional properties of the reference antibody are the inherent property of the reference method. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art method is different from the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/13/03 have been fully considered but are not found persuasive.
Applicants' position is that (1) applicants' claimed methods comprise administering a whole, non-endogenous CETP to a mammal to achieve an anti-atherogenic condition characterized by a heretofore unknown levels of CETP molecules, CETP activity, HDL-cholesterol, or LDL-cholesterol in the blood of the mammal, (2) the WO 96/39168 publication (hereinafter, "Kwoh") does not teach administering a whole non-endogenous CETP protein, (3) the peptide vaccines of Kwoh are not reported to provide a blood plasma condition in which the level of CETP activity in a mammal fall below 20% of the level found in the untreated mammal, (4) the examiner provides no explanation for the interpretation of the claim term "less than about 10%" as being met by the best case 16% LDL/Total cholesterol calculated from Kwoh Table 1 data, Applicants submit that the term "less than about 10%" sets a threshold including only values under 10% up to and not significantly exceeding 10%, (5) only by using a whole non-endogenous CETP immunogen according to Applicants' disclosure can such a low level of LDL-cholesterol be achieved.

Contrary to applicant's assertion that the WO 96/39168 publication does not teach administering a whole non-endogenous CETP protein, the WO 96/39168 publication teaches administering a whole non-endogenous CETP (See Summary of the Invention on page 2). In fact, claim 47 recites non-endogenous CETP in which the amino acid seuqence has been altered by deletion, or substitution of one or more amino acids.

The WO 96/39168 publication further defines the "the protein or peptide to be administered can be all or part of the CETP protein, so long as the protein or peptide contains a B cell and/or T cell epitope. As used herein, "CETP peptide" is intended to include both the full length CETP amino acid sequence as well as fragment." (See page 5, lines 12-16, claim 2 of WO 96/39168 publication, in particular). In response to the allegation that the examiner provides no explanation for the interpretation of the claim term "less than about 10%", applicant is directed to previous Office Action mailed 1/29/02. The reference method decreases LDL-cholesterol to less than 16% of the total cholesterol in the serum (blood plasma), which is less than 20% (See Table 1, page 11, in particular). Further, the term "% of untreated control" is relative and does not taken into consideration of individual variation. Finally, while the reference is silent that the

reference method of administering to the mammal a whole non-endogenous CETP has the property of that recited in claims 41-43 and 45, the antibody directed against said non-endogenous CETP in the mammal and the functional properties of the reference antibody are the inherent property of the reference method. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art method is different from the claimed method. In the absence of a side-by-side comparison, applicants' arguments were not found persuasive.

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